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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,164	CARTLIDGE, SUE ANN	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/6/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,17-19,21-25,40,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15, 17-19. 21-25, 40 and 42-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 6, 2007 has been entered.

2. Claims 15, 17-19. 21-25, 40 and 42-43 are pending and are being acted upon in this Office Action.

3. Claim 15 is objected to because it is unclear as to which epitope the claimed antibody binds. Is it the KDR/Flk-1 that the antibody binds or the epitope consisting of the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2? Further, the close language "peptide *consisting* of an amino acid sequence of KDR/FLK-1" and the open-language of "the amino acid sequence *comprises* SEQ ID NO: 1 or SEQ ID NO: 2" is confusing. Clarification is required.

4. The following rejections remain.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 15, 17-19, 22-25, and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al (of record, EMBO J 20(11): 2768-2778, June 2001; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-153).

Takahashi et al teach a method of making antibody such as polyclonal antibody that bind to KDR/Flk-1 comprising the amino acid sequence of the claimed unphosphorylated peptide consisting of SEQ ID NO: 2 and the reference antibody detects activation of KDR/Flk-1 receptor

by VEGF-A binding to the tyrosine residue Y1175 of the KDR/Flk-1 receptor. The reference method comprises immunizing an animal such as a rabbit with a phosphorylated peptide such as VCDPDKFHYDNTAG surrounding phosphorylated Y1175 and isolating antibody from the animal (see page 2776, col. 1, Rabbit anti-phosphoY1775 polyclonal antibody, in particular). Takahashi et al also teach tyrosine residues (Y) at position 1175 (Y1175) and **(Y1214)** of the KDR/Flk-1 receptor are the two major VEGF-A dependent autophosphorylation sites *in vitro* and *in vivo* (see abstract, page 2770, col. 1, first paragraph, in particular). Takahashi et al also teach phosphorylation of Y1175 is via MAP kinase (see page 2771 col. 1, in particular) but phosphorylation of Y1214 is not, suggesting that tyrosine phosphorylation of Y1214 may be important for other signaling pathways of VEGF-A in endothelial cells such as the stimulation of chemotaxis, cell survival, or the regulation of gene expression (see page 2775, in particular). Takahashi et al further teach peptide such as VCDPKFHYDNTAG surrounding the Y1214 (see page 2769, col. 2, Figure 1, in particular) and providing motivation to the skilled artisan to make antibody using phosphospecific peptide surrounding the tyrosine residue 1214 of interest to make antibody that is highly specific and distinguishable from other tyrosine residue and kinase receptors (see page 2774, col. 2, in particular). Takahashi et al teach antibody to phosphotyrosine (anti-PY) is useful for detection of activated KDR/Flk-1 receptor, not only in the western blotting but also in histological sections (see paragraph bridging page 2771 and 2772, in particular) and potentially for use alone or in combination with a KDR/Flk-1 tyrosine kinase inhibitor (see page2774, col. 2, in particular). Takahashi et al also teach carrier such as phosphate-buffered saline (PBS) and composition comprising anti-BrdU and PBS (see page 2776, col. 2, Immunocytochemistry, page 2777, col. 1, first paragraph, in particular). Although Takahashi et al does not teach the specific antibody to Y1214 of the KDR/Flk-1 receptor, Takahashi et al do in fact teach epitope surrounding Y1214 such as peptide VCDPKFHYDNTAG are well conserved in the C-terminal region of KDR/Flk-1 in various mammalian species (see page 2769, col. 1, results, in particular), and the reference VCDPKFHYDNTAG is nearly identical to the claimed phosphorylated peptide of SEQ ID NO: 1 (VCDPKFHYDNTAGS) and unphosphorylated peptide of SEQ ID NO: 2 (VCDPKFHYDNTAGS). Clearly, one having ordinary skill in the art would have been motivated with the expectation of success from the teachings of Takahashi et al to make antibody such as polyclonal antibody that is highly specific to the phosphorylated tyrosine residue Y1214 of KDR/Flk-1 by substituting the peptide QQDGKYIVLPI surrounding PY1175 as immunogen for the other peptide VCDPKFHYDNTAG surrounding PY1214 as

taught by Takahashi et al, then immunizing an animal with said peptide and isolating the antibody from the animal.

The invention in claim 17 differs from the teachings of the reference only in that the antibody is a monoclonal antibody instead of polyclonal antibody.

Harlow et al teach a method of making monoclonal antibody to any antigen of interest. Harlow et al further teach the advantages of monoclonal antibody are that the source of antibody will be unlimited, their binding specificity and their homogeneity (see page 141, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make monoclonal antibody as taught by the Harlow et al using the phosphopeptide VCDPKFHYDNTAG surrounding phosphor tyrosine PY1214 of the KDR/Flt-1 receptor as immunogen as taught by Takahashi et al to produce a monoclonal antibody that binds to the activated KDR/Flt-1 receptor comprising the amino acid sequence VCDPKFHYDNTAG to detects activation state of the KDR/Flk-1 receptor. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow et al teach the advantages of monoclonal antibody are that the source of antibody will be unlimited, their binding specificity is monospecific and the antibody is homogeneous (see page 141, in particular). Takahashi et al teach tyrosine residues (Y) at position 1214 (Y1214) of the KDR/Flk-1 receptor is one of the two major VEGF-A dependent autophosphorylation sites *in vitro* and *in vivo* and phosphospecific peptide such as VCDPKFHYDNTAG surrounding PY1214 is useful for making antibody that is highly specific and distinguishable from other tyrosine residue and kinase receptors (see page 2774, col. 2, in particular). Takahashi et al teach antibody to phosphotyrosine (anti-PY) is useful for detection of activated KDR/Flk-1, not only in the western blotting but also in histological sections (see paragraph bridging page 2771 and 2772, in particular) and potentially for use alone or in combination with a KDR/Flk-1 tyrosine kinase inhibitor (see page 2774, col. 2, in particular). Once the antigen of interest is selected, the use of that antigen in the known method of Kohler and Milstein will result in the expected hybrid cell lines and the specific monoclonal antibodies. Ex parte Erlich, 3 USPQ2d 1011, 1015 (BPAI 1986). Claim 19 is included in this rejection because it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to substitute the anti-BrdU in a composition comprising and anti-BrdU and PBS for the polyclonal

antibody that binds specifically to PY1214 of KDR/Flk-1 for detection of activation of KDR/Flt-1 receptor as taught by Takahashi et al. Because activated KDR receptor comprises the phosphorylated Y1214 epitope of SEQ ID NO: 1, the reference antibody made with the phosphopeptide VCDPKFHYDNTAG obviously also binds to the activated KDR receptor comprising the phosphorylated Y1214 epitope VCDPKFHYDNTAG within the KDR receptor as well as the phosphorylated peptide sequence of the claimed SEQ ID NO: 1 because of the nearly identical sequence. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best. 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

Applicants' arguments filed 4/4/07 have been fully considered but are not found persuasive.

Applicants' position is that claim 15 has been amended to include features of claims 41, 42, and 43 as discussed above. Applicants respectfully submit that claims 41, 42, and 43 were not included under these rejections. Accordingly, these rejections are not applicable to claim 15 and its dependent claims.

In response, the amendment to claim 15 "antibody that binds a peptide consisting of an amino acid sequence of KDR/Flk-1, wherein the amino acid sequence comprises SEQ ID NO: 1 or SEQ ID NO: 2" appears to broaden out the binding specificity of the claimed antibody. This is because the term "comprising" is open-ended. It expands the peptide of SEQ ID NO: 1 or SEQ ID NO: 2 to include additional amino acids at either or both ends to read on the KDR/Flt-1 receptor. Further, Because activated KDR receptor comprises the phosphorylated Y1214 epitope of SEQ ID NO: 1, the reference antibody made with the phosphopeptide VCDPKFHYDNTAG obviously also binds to the activated KDR receptor comprising the phosphorylated Y1214 epitope VCDPKFHYDNTAG within the KDR receptor as well as the phosphorylated peptide sequence of the claimed SEQ ID NO: 1 because of the nearly identical sequence. Takahashi et al teach epitope surrounding Y1214 such as peptide VCDPKFHYDNTAG are well conserved in the C-terminal region of KDR/Flk-1 in various mammalian species (see page 2769, col. 1, results, in particular), and the reference VCDPKFHYDNTAG is nearly identical to the claimed phosphorylated peptide of SEQ ID NO: 1 (VCDPKFHYDNTAGS), see page 2769, col. 2, Y1214 and unphosphorylated peptide of SEQ ID NO: 2 (VCDPKFHYDNTAGS). Since the Patent

Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best. 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

7. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al (of record, EMBO J 20(11): 2768-2778, June 2001; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-153) as applied to claims 15, 17-19, 22-25, and 42-43 mentioned above and further in view of US 6,204,011 (filed June 17, 1998; PTO 892).

The combined teachings of Takahashi et al and Harlow et al have been discussed supra.

The invention in claim 21 differs from the teachings of the references only in that a kit for comprising a probe that detects activation of the KDR/Flt-1 receptor and binds tyrosine residue Y1214 of the KDR/Flk-1 receptor.

The '011 patent teaches a kit comprising antibodies that bind to human KDR and all the essential reagents required to perform various assays such as detection assays specific for commercial expedience (see col. 21, lines 65-66, col. 22, lines 5-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody that binds to KDR in the kit as taught by the '011 patent for the polyclonal antibody or monoclonal antibody that binds to Y1214 of the activated KDR/Flk-1 receptor comprising the peptide sequence VCDPKFHYDNTAG as taught by Takahashi et al and Harlow et al. A kit will allow for ease of use for the practitioner since all the essential reagents, and standard for use are included in a kit as taught by the '011 patent (see col. 15, lines 54-61, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed 4/4/07 have been fully considered but are not found persuasive.

Applicants' position is that claim 15 has been amended to include features of claims 41, 42, and 43 as discussed above. Applicants respectfully submit that claims 41, 42, and 43 were not included under these rejections. Accordingly, these rejections are not applicable to claim 15 and its dependent claims.

In response, the amendment to claim 15 "antibody that binds a peptide consisting of an amino acid sequence of KDR/Flk-1, wherein the amino acid sequence comprises SEQ ID NO: 1 or SEQ ID NO: 2" appears to broaden out the binding specificity of the claimed antibody. This is because the term "comprising" is open-ended. It expands the peptide of SEQ ID NO: 1 or SEQ ID NO: 2 to include additional amino acids at either or both ends to read on the KDR/Flt-1 receptor.

8. New Grounds of Rejection are following.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,766,860 (issued June 16, 1998; PTO 892).

The '860 patent teaches an antibody such as polyclonal antibody that binds to the amino acid sequence of KDR wherein the amino acid sequence comprises SEQ ID NO: 8 that comprises the residues 1209-1220 of the claimed sequence of SEQ ID NO: 2 (see reference SEQ ID NO: 8, col. 12, lines 41-65, in particular). The term comprising is open-ended. It expands the claimed peptide to include additional amino acids at either or both end to include the reference SEQ ID NO: 8. Thus, the reference teachings anticipate the claimed invention.

11. Claims 15, 17-19, and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 6,204,011 B1 (issued March 20, 2001; PTO 892).

The '011 patent teaches various antibodies such as monoclonal antibody and polyclonal antibody that binds to the amino acid sequence of KDR wherein the amino acid sequence comprises SEQ ID NO: 2; the reference full-length KDR comprises the residues 1209-1220 of the claimed SEQ ID NO: 2 (see reference SEQ ID NO: 2, residues 1209-1220, col. 17, line 25 through col. 18, line38, in particular). The '011 patent further teaches a kit comprising the reference antibody (see col. 21, line 65-67, in particular). The '011 patent teaches a method of

generating the reference antibody by immunizing an animal such as a mouse or a rabbit with human KDR and isolating the antibody from the animal (see col. 17, line 19-45, in particular). The '011 patent teaches a composition comprising the reference antibody as antagonist and a pharmaceutical acceptable carrier such as phosphate buffer (see col. 22, lines 13 through col. 23, col. 18, line 39-57, in particular). The term comprising is open-ended. It expands the claimed peptide to include additional amino acids at either or both end to include the reference SEQ ID NO: 2. Thus, the reference teachings anticipate the claimed invention.

12. Claims 15, 17-19, 22-23, and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,840,301 (issued November 24, 1998; PTO 892).

The '301 patent teaches an isolated monoclonal antibodies such as DC101 that binds to mouse Flk-1 or human KDR comprising an amino acid sequence of Flk-1 or KDR such as the extracellular domain of Flk-1/KDR (see summary of invention, col. 6, lines 50-57, col. 7, line 28-36, in particular). The '301 patent also teaches a method of preparing various antibodies such as monoclonal antibodies, polyclonal antibody that binds to human KDR comprising an amino acid sequence such as the extracellular domain of KDR (see col. 7, line 11 through col. 8, line 36, in particular). The term "comprising" is open-ended. It expands the peptide of SEQ ID NO: 2 to include additional amino acids to read on the full-length KDR/Flk-1 receptors as well as the extracellular domain of KDR/Flk-1 receptor. The '301 patent teaches antibody binding fragment such as $F(ab')_2$, Fab and single chain Fv fragment (see col. 8, lines 4-16, in particular). The reference also teaches a composition comprising the reference antibody and a pharmaceutically acceptable carrier (see col. 3, line 5-7, in particular). Thus, the reference teachings anticipate the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,204,011 B1 (issued March 20, 2001; PTO 892) in view of Harlow et al (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629).

The teachings of the '011 patent have been discussed supra.

The invention in claim 40 differs from the teachings of the reference only in that the antibody is a $F(ab')_2$, a Fab or a single chain Fv.

Harlow et al further teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce antibody fragment as taught by Harlow *et al* with the polyclonal or monoclonal antibody that binds to KDR as taught by the '011 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody and antibody fragment because Harlow *et al* teach that fragments of antibodies can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular).

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Patent Examiner
Technology Center 1600
January 22, 2008